REMARKS/ARGUMENTS

I. Preliminary Remarks

The Examiner requested copies of the references cited in Form PTO-1449, submitted on February 20, 2002. As indicated in the information disclosure statement, all (82) references can be found in corresponding U.S. patent application Serial No. 09/462, 819. The Examiner indicated in a phone conversation with the undersigned on February 2, 2004 that he would obtain the references from the corresponding application.

The Applicants would first like to provide a brief description of the invention as claimed. In one aspect, the invention provides methods of treating certain recited disease states through administration of a micelle composition prepared by a method comprising the steps of (i) mixing one or more lipids (wherein at least one lipid component is bonded to a water soluble polymer) with a biologically active member of the VIP/glucagons/secreting family of peptides (including fragments and analogs thereof), and (ii) forming sterically stabilized micelles under conditions wherein the biologically active compound becomes associated with the micelle in a more biologically active confirmation. See claim 5.

In another aspect, the first step in the method of production, the mixing step, is carried out in an organic solvent and includes at least one lipid component conjugated to a targeting agent, and the second step is carried out by (a) removing the organic solvent to leave a dry film and (b) hydrating the dry film in an aqueous solution. This aspect further includes a step of incubating the micelles prepared in this manner under conditions such that the targeting compound assumes an active confirmation. See claim 6.

II. The Outstanding Rejections

The Examiner rejected claims 5-6 and 10-12 under 35 U.S.C. §112, first paragraph, for assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 5-6 and 10-12 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure of U.S. Patent No. 5,376,637 to Sawai *et al.* [hereinafter "Sawai"] in combination with the disclosure of Trubetskoy et al. Proceed. Intern. Symp. Control. Rel. Bioact. Mater. 22:452-453, 1995

[hereinafter "Trubetskoy"] and either the disclosure of U.S. Patent No. 5,376,156 to Burke [hereinafter "Burke"] or the disclosure of European Patent Application No. 0721776 to Sakurai et al. [hereinafter "EP 0721776"] or the disclosure of Zhang et al., Internat. J. Pharmaceutics 132:195-206, 1996 [hereinafter "Zhang"] .

III. Patentability Arguments

A. The Rejection of Claims 5-6 and 10-12 under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 5-6 and 10-12 under 35 U.S.C. §112, first paragraph, for assertedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected , to make and/or use the invention.

The Examiner asserted that (1) the instant claims are drawn to the treatment of 26 disease conditions, (2) many of which are not even connected, (3) the causes of many of the claimed diseases are not known, and (4) many are poorly understood. The Examiner asserted that the Applicants have provided no definition or explanation as to what comes under the category of "peptide fragments and analogs" as cited in claim 5, and that there is an unpredictability in the art. The Examiner also asserted that the Applicants have provided no examples either in vitro or in vivo for the variety of disease conditions claimed, and because there is unpredictability in the art of the treatment of the claimed diseases using the free active agents themselves, treatment of diseases using micelles containing active agents claimed is also unpredictable. The Examiner further asserted that broad claims, in the absence of such support, would require undue experimentation by one of ordinary skill in the art to select an active agent and practice the invention. The Applicants respectfully disagree.

First, "peptide fragments and analogs" as cited in claim 5 are terms that are well known to one of skill in the art and need no definition. For example, a peptide fragment as used in claim 5 would be a smaller part one of the peptides of the VIP/glucagon/secretin family of peptides. The art is rife with examples of various fragments and analogs of peptides in the VIP/glucagons/secretin family (see Exhibit A). VIP fragments are commercially available (see page 38, lines 6 through 8 and Exhibit A) and were used in experiments performed in Example 6, page 46, line 4, through page 47, line 4, of the instant application. Fragments and analogs of the VIP family of peptides are known and used by those of skill in the art in a variety of scientific experiments and medical therapies (see Exhibit A).

Second, the art is replete with examples of the use of the VIP/glucagons/secretin family of peptides in the treatment of a wide variety of pathologies as claimed in the instant invention, which, as noted by the Examiner, do not have apparent connection. Regardless, these pathologies have been treated with the VIP/glucagons/secretin family of peptides. Accordingly, the Applicants have provided published scientific abstracts (see Exhibit B) which discuss the use of members of this family of peptides in the treatment of pathologies such as, but not limited to, asthma, AIDS, impotence, acute esophageal food impaction, autism, and arthritis (see Exhibit B). These documents and results in the specification, showing therapeutic effectiveness of micelles made by the recited method, support the Applicants' position that micelles of this type are effective for treatment of the recited conditions. If the Examiner requests additional information to support this position, please advise the Applicants.

Based on the foregoing remarks, the rejection of claims 5-6 and 10-12 under 35 U.S.C. §112, first paragraph, should be withdrawn.

B. The Rejection of Claims 5-6 and 10-12 under 35 U.S.C. §103(a)

Claims 5-6 and 10-12 were rejected under 35 U.S.C. §103(a) for being directed to subject matter allegedly rendered obvious by the disclosure Sawai in view of the disclosure of Trubetskoy and either Burke or EP 0721776 or Zhang. The Examiner asserted that Sawai discloses the use of pharmaceutical compositions comprising VIP and a surfactant in a method of treating asthma. However, Sawai does not specifically discuss the use of micelles containing VIP, although surfactants may form micelles in aqueous solutions. The Examiner also asserted that Trubetskoy discloses that polymer-derivatized lipids such as PEO-phosphatidylethanolamine form micelles and such micelles can be used to solubilize poorly soluble or amphipathic substances; however, the Examine also acknowledged that the active agent was not added after the formation of micelles. The Examiner went on to cite Burke, Zhang, and EP 0721776 for disclosing processes of preparing micelles where the active agent is loaded to the micelles after micelle preparation. The Examiner asserted that the use of PEG containing polymeric compounds as the carrier of amphipathic VIP of Sawai for the treatment of asthma would have been obvious to one skilled in the art since Trubetskoy discloses that these compounds form micelles and solubilize poorly soluble or amphipathic compounds. The Examiner further asserted that one skilled in the art would be motivated to use this surfactant since PEG appears to increase the blood circulation time of

drug carrier systems as evidenced from the teachings of Zhang, and the addition of VIP after the formation of micelles would have been obvious to one of ordinary skill in the art since the references of Burke, Zhang, and EP 0721776 all show that the active agent can be loaded onto micelles.

In response, the Applicants respectfully traverse. In order to render a claimed invention obvious, the cited art not only has to (1) teach or suggest every element of the claimed invention, the cited reference, or combination of references, (2) must also provide some suggestion or motivation to modify the reference(s) to arrive at the claimed invention and (3) there must be some reasonable expectation of the success of such modification of the reference(s). In re Vaeck, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). The motivation and the reasonable expectation of success must come from the art and not from the Applicants' own disclosure. As stated in MPEP 2143, all three of the above criteria must be met in order to properly establish prima facie obviousness. The Applicants submit that the disclosures of Sawai, Trubetskoy, Burke, EP 0721776, and Zhang fail to meet the criteria for establishing prima facie obviousness in view of the fact that the combination of references fails to demonstrate (i) production of a *sterically stabilized micelle* product which includes a *biologically active member of the VIP/glucagons/secretin family of peptides* used in the (ii) *treatment of any of the disease states recited*, for example, in claim 5.

The disclosure of Sawai describes the use of VIP in a surfactant in the treatment of asthma, but, as the Examiner points out, it is silent with respect to the use of VIP with a sterically stabilized micelle. The disclosure of Trubetskoy describes the preparation of micelles, wherein a lipid component is bound to a water soluble polymer, such as PEO-phosphatidylethanolamine in order to promote solubilization of a drug that poorly soluble in aqueous solution; however, the reference says nothing about whether the solubilized drug associates with the micelle in an active conformation. The disclosures of Burke, Zhang, and EP 0721776 describe the addition of compounds to preformed micelles, but Burke, Zhang, and EP 0721776 are silent as to the use of sterically stabilized micelles and whether biological activity can be maintained in such compounds in association with the micelles. For example, Burke describes the addition of 10,11-methylenedioxycamptothecin to preformed micelle suspensions, but the disclosure is silent with respect to use of sterically stabilized micelles in this process. Moreover, Burke is silent as to whether the resulting 10,11-methylenedioxycamptothecin/micelle composition is biologically active. Zhang describes loading of taxol to a preformed micelle, but the disclosure is silent as to whether the

resulting taxol/micelle compositions are biologically active. EP 0721776 describes loading of salmon testes DNA to a preformed micelle with a chargeable and a non-chargeable segment. Similarly, EP 0721776 is silent as to whether the resulting DNA/micelle compositions are biologically active.

One of the essential features of the present invention is that the micelles produced by the recited method must be *sterically stabilized* (wherein at least one lipid component of the bilayer is attached to a water soluble polymer). Moreover, the resulting micelle must be *biologically active* with respect to the compound that is loaded. In the disclosures of Sawaii, Trubetskoy, Burke, Zhang, or EP 0721776, there is no indication that these same compounds would be active if one or more of the lipids of the bilayer is bound to a polymer. Polymer attachment to a micelle necessarily gives rise to steric hindrance, as well as physical changes in the localized environment at the local exterior of the micelle. Whether or not a compound in this polymer-rich environment would maintain a proper biological conformation, or be able to interact with a biological ligand cannot be predicted from the cited references since, and neither Sawaii, Trubetskoy, Burke, Zhang, nor EP 0721776 suggests that such a micelle composition would be biologically active. As a result, the combination of references offers only an invitation to carry out the recited method aspect of the invention, and less than a reasonable expectation of success for producing the resultant biologically active micelle product. Moreover, in failing to provide sufficient disclosure for producing the recited micelle, it is axiomatic that the references also fail to disclose or suggest treatment of the variously recited disease states with such a micelle product.

While the combination of the references cited by the Examiner may individually include one or more of the elements of the presently claimed invention, the combination fails to suggest implicitly or expressly the method of micelle production aspect of the invention as a whole. The Applicants submit that the Examiner's assertion that it would have been obvious for one of skill in the art to combine these references and conduct the steps of the claims 5-6 and 10-12 to treat a pathology is merely hindsight.

Based on the foregoing reasoning, the Applicants submit that the Examiner has not established a *prima facie* case of obviousness for any of the claims standing rejected under § 103(a). Because of the failure of the combined references to render obvious claim 5, the dependent claims are also non-obvious. Accordingly, the rejection of claims 5-6 and 10-12 under 35 U.S.C. § 103(a) over Sawai in view of Trubetskoy and either Burke or EP 0721776 or Zhang has been overcome and should be withdrawn.

SUMMARY

In view of the remarks made herein, the Applicants believe that claims 5-6 and 10-12 are in condition for allowance and request expedited notification of the same.

Respectfully submitted,

MARSHALL, GERSTEIN & BORUN LLP
6300 Sears Tower
233 South Wacker Drive
Chicago, IL 60606
(312) 474-6300

By: 
Lynn L. Jaulis
Reg. No: 53,066

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